Pharmaco-informatics: Accelerated NPEM Population Pharmacokinetic Modeling, "Maximum Entropy" (ME) Parameter Distributions, and new "Multiple Model" (MM) Stochastic Dosage Regimens now by Oral, IM, and both Intermittent and Continuous IV.

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ABSTRACT

New techniques have greatly increased the speed of NPEM population analysis 20 to 30-fold. Development of ME parameter distributions now permits use of literature population parameter values to create discrete probability density functions (PDF's) for MM dosage design. The MM regimens are no longer limited to the continuous IV route, but have now been extended to include all common routes. NPEM population analysis is much more practical and feasible. ME parameter distributions now permit informed yet sceptical use of literature data of drug behavior. The full implementation of MM stochastic control of dosage regimens by all routes now permits essentially full use of information, either in an NPEM or ME population pharmacokinetic model, to achieve and maintain selected therapeutic goals with maximal precision, including after Bayesian updating of parameter PDF's as serum drug levels are obtained.

INTRODUCTION

Previous work showed the utility of NPEM population pharmacokinetic modeling, with discrete support points for the population joint probability density function (PDF). These points become multiple contending patient models to use to plan the initial MM dosage regimen for a new patient, and to update as feedback becomes available. This process has now been extended by means of accelerated NPEM algorithms, by use of ME discrete PDF's, and by the implementation of all usual routes of drug administration in the MM stochastic control strategy.

METHODS

NPEM modeling has been accelerated by the observation that once a point in the joint parameter PDF reaches a probability at or below 10^{-10}, that point never again reaches a significant value. Such points can thus be neglected in subsequent cycles of the NPEM algorithm, which now gets progressively faster. Further, at periodic intervals one can extrapolate forward, using the rate of change of probability of a point from one cycle to another, to compute the PDF log likelihood at 10, 50, and 70 cycles into the future, and go to the most likely PDF. These 2 techniques have resulted in a 20 to 30-fold increase in speed for the NPEM population modeling program. This new version is now in use in the USC*PACK programs.

ME discrete PDF's can be computed within stated parameter ranges which satisfy constraints of the parameter means and standard deviations. This permits development of discrete PDF's based on literature data which can be used as population priors for MM stochastic dosage design, and for Bayesian updating of that PDF when feedback of measured serum levels becomes available.

The implementation of the MM stochastic control strategy by all common routes of administration has now been accomplished.

RESULTS AND CONCLUSIONS

NPEM population modeling of large data sets can be done in hours instead of days. ME population models now permit literature data of drug behavior to be used for MM stochastic dosage design when NPEM models are not available. The full implementation of the MM control strategy by all common routes now permits this method to be applied to all common problems of therapy with potentially toxic drugs. A clinical graphical user interface for these programs is in development.

The current programs run on PC's and use analytic solutions to the differential equations. Extension of these approaches to analysis of larger and nonlinear pharmacokinetic and dynamic models will probably require the use of supercomputers.

Acknowledgements

Supported by NIH grant LM 05401, and by the Stella Slutzky Kunin Research Fund.